81. (Amended) A cell line derived from cells obtained from an animal made by the method of claim *[75]* 76.

REMARKS

Status of the Claims

As filed, the instant application contained claims I - 47. A Preliminary Amendment was filed February 13, 2002 wherein claims 1 - 47 were cancelled and new claims 48-81 were added. In accordance with the instant Amendment, claim 63 has been cancelled. Cancellation is not intended, and should not be construed, in any manner to restrict Applicant's right to pursue such canceled claims, or the subject matter thereof, in this application or any application claiming priority from or through this application, or in any reissue, reexamination or similar application which may be filed with respect thereto. Thus, claims 48- 62 and 64 - 81 are now pending in this application.

Claims 48, 52-54, 56, 57, 59, 60, 64-68, 70-75 and 78-81 have been amended. Support for the amendments to the claims is found in numerous places in the specification, and in the claims as filed. Accordingly, no new matter has been added. No additional fee is required.

Rejections of the Claims

Rejections under 35 U.S.C. § 101 The Examiner has rejected claims 53, 54, 56, 57, 65, 67, 68, 71, 73, 74, 77, 79, and 80 under 35 U.S.C. §101 as being directed to non-statutory subject matter as being drawn to embodiments encompassing humans. Attention is directed to the amendments

to the claims in question wherein the claims have been amended to recite "non-human" where appropriate. Consequently, Applicants submit that the stated ground of rejection has been rendered moot and respectfully request that the same be withdrawn.

Rejections under 35 U.S.C. § 112 ¶1 The Examiner has rejected claims 48, 52, 59 - 64, 70 and 76 under 35 U.S.C. §112, ¶ 1 as allegedly not being enabled for methods where the donor nucleus and recipient oocyte are of different species. Attention is directed to claims 48 and 59, wherein the claims have been amended to recite that the donor cells or nuclei, recipient oocyte, and host animal are "of the same species." Applicants further point out that claim 70 already recites that the donor nucleus or cell, recipient oocyte and host animal are "of the same species," thus traversing the ground of rejection recited in the Action. With respect to claim 76, and claims dependent therefrom, the claims, as filed, recite that the blastocysts obtained through steps (a) through (g) of the claimed method are transferred in step (h) to a medium "capable of allowing the one or more blastocysts to develop into a viable animal." Applicants respectfully submit that, one of skill in the art would understand that the claim as written would inherently encompass the concept now explicitly recited in amended claims 48 and 59. Accordingly, no further amendment to the claims is required to bring them into compliance with §112, ¶ 1. Applicants respectfully submit that the stated ground of rejection has been mooted and further request withdrawal of same.

Rej ctions under 35 U.S.C. § 112, ¶ 2 The Examiner has rejected claims 50 and 52 under 35 U.S.C. §112, ¶ 2 on the alleged basis that claim 52 does not display antecedent basis to claim 50, in that there is no "subpopulation" recited in that claim.

Applicants direct attention to claim 52 amended changing its dependency to claim 51, thus providing an antecedent basis in accord with §112, ¶ 2. Consequently, Applicants respectfully request the withdrawal of the rejection under this statutory section.

Rejections under 35 U.S.C. § 102(b).

The Examiner has rejected claims 48, 49, 51, 52, 59 - 61 and 70 under 35 U.S.C. §102(b) as allegedly being anticipated by Cibelli *et al.* Applicants respectfully traverse this ground for rejection.

The Examinercharacterizes Cibelli *et al.* as disclosing the production of cloned transgenic calves by a method that includes a step of culturing the fused cells "to greater than a 2-cell embryo." Although not explicitly stating so, Applicants assume for the sake of these remarks that the Examiner is stating that the culture conditions disclosed in the cited reference inherently include a plurality of culturing passages. Applicants respectfully disagree with such a presumption, if that is indeed the position being taken by the Examiner. Furthermore, attention is directed to amended claims 48, 59, 60, and 70 that now recite that the population of cells is cultured through at least five passages, thus providing sufficient opportunity to introduce genetic manipulations into the cultured cells, and optionally confirming the presence of those genetic

modifications. Furthermore, attention is directed to the specification, at pp. 23 - 24 wherein specifics of the cell culturing conditions of the methods of the claimed invention are provided in some detail. Mentioned specifically on p. 24, ll. 23-24, a single culturing passage lasts for approximately six days. In comparison, note 12, p. 1258 of the Cibelli *et al.* reference cited in the Action discloses incubation of fused embryos for a period of 6.5 days. In contrast, the method of the present invention contemplates culturing donor cells for at least five culturing passages that, in accord with the specific teachings of the specification cited above, would require at least 30 days of culturing **prior to** fusion of the donor cells with recipient enucleated oocytes. This is also in direct contrast with the , accepted teachings of the prior art that required fresh cells as donors of nuclear material.

A major shortcoming of the prior art practice, one that is successfully addressed by the instant invention, is that it is practically impossible to achieve and confirm genetic modifications to the donor cells prior to fusion with recipient oocytes. Thus, Applicants submit that the claims as amended are clearly distinguishable from the teachings of the cited Cibelli *et al.* reference and request that the stated ground of rejection be withdrawn.

The Action has also rejected claims 53-58, 71-75 and 77-81 under 35 U.S.C. §102(b) as allegedly being anticipated by the Cibelli *et al.* reference. Applicants also respectfully traverse this ground of rejection.

Claims 53 - 58 are directed to various embodiments derived from the practice of the method of claim 48. Likewise, claims 71 - 75 are directed to various embodiments derived from the practice of the method of claim 70. In a

fashion similar to claim 48, claim 70 now recites that donor cells are cultured prior to fusion with recipient oocytes for at least 5 culturing passages. In a similar fashion, claims 77 - 81 are directed to various embodiments derived from the practice of the method of claim 76. Claim 76 specifically recites that the diploid donor cell of the method is cultured for at least 20 cell doublings, which culturing, according to the disclosures of the specification, would entail approximately 10 culturing passages. Thus, Applicants submit that the logic of the above remarks as applied to claim 48 and related claims applies equally well to claims 53 - 58, 71 - 75, and 77 - 81. Thus, Applicants respectfully submit that the stated grounds of rejection have been obviated and request withdrawal of same.

The Examiner has rejected claim 63 under 35 U.S.C. § 102(b) as allegedly being anticipated by Presicce *et al.* Attention is directed to the above amendment cancelling claim 63 without prejudice, thus rendering the stated ground of rejection moot.

The Examiner has rejected claims 65 - 69 under 35 U.S.C. §102(b) as allegedly being anticipated by Plump *et al.* Applicants respectfully traverse this ground of rejection.

The Examiner characterizes the Plump *et al.* reference as disclosing transgenic mice whose genome comprises a disruption in an apo-E gene such that functional apo-E is not produced. According to the Examiner, the cells and organs obtained from, the teachings of the Plump *et al.* reference "are not patentably distinct from the cells claimed." The logic presented by the Examiner fails to consider the method by which the cells, organs and tissue of

the claimed invention are obtained, particularly in comparison the methods disclosed in the cited reference, as well as the species of animal and type of cell used for nuclear donation. All of the claims against which the Examiner has cited the Plump *et al.* reference depend from independent claim 64, a claim that the Examiner has not rejected over the Plump *et al.* reference. Applicants respectfully submit that as claim 64 is not rejected as anticipated by the Plump *et al.* reference and the rejection of claim 64 under 35 U.S.C. 112 ¶1 has been avoided (supra), claim 64 and the claims dependent thereon (claims 65-69) are allowable to the applicants and this should now be so indicated.

It is noted that the method of independent claims 65-69 all are "product by process claims" and hence incorporate the limitations of claim 64. As claim 64 is allowable to applicants, so are claims 65-69.claim 64 involves the long-term passage (at least five culturing passages) of donor cells, which long-term culturing makes possible the introduction of targeted genetic alterations and the selection of transformed cells displaying stable phenotypic traits attributable to such genetic alteration. In contrast, the disclosure of the Plump *et al.* reference is silent on the extent of culturing of transformed donor cells. Moreover, Plump *et al.* specifically disclose that the donor cells are mouse embryonic stem (ES) cells, and not the somatic cells of the claimed invention. As a consequence, the disclosure of the Plump *et al.* reference cannot anticipate the relevant claims of the present invention, and Applicants respectfully request that the cited ground of rejection be withdrawn.

Rej ctions under 35 U.S.C. § 103(a) The Examiner has rejected claims 48, 50, 60, 62, and 76 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cibelli *et al.*, in view of Arbones *et al.* and Plump *et al.* Applicants respectfully traverse.

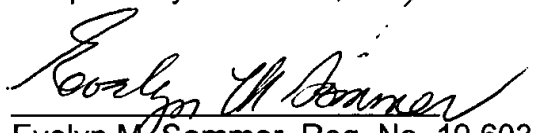
The Examiner contends that "it would have been obvious to the ordinary artisan at the time of the instant invention to produce a bovine comprising a disruption in an apo-Egene by nuclear transfer as taught by Cibelli, where the differentiated donor cell had been cultured through 100 doublings as taught by Arbones, and where the differentiated donor cell comprised a disruption apo-E such *[sic]*." Contrary to the position espoused by the Examiner, the cited references fall far short of leading one of skill in the art the claimed invention. First of all, as addressed above, the teachings of Cibelli *et al.* fail to disclose or suggest, contrary to accepted prior art practices, culturing donor cells for multiple passages (five or more) **prior to** fusion of genetic material from the donor cells with enucleated recipient oocytes. Also, as specifically discussed above, the Plump *et al.* reference discloses the use of mouse embryonic stem cells solely, a type of cell that Is widely recognized in the art (as discussed in the instant specification and in the cited references) as being far more specifically suited to the type of manipulations required for the practice of the claimed invention. With respect to the disclosure of the Arbones et al. reference, there is nothing in that disclosure that would suggest to one of skill in the appropriate art that myoblast cells cultured for at least 100 doublings (50 culturing passages) prior to transformation to achieve genetic alterations through homologous

recombination. Furthermore, the only disclosure of that reference dealing with fusion of donor genetic material with recipient oocytes involves the use of mouse embryonic stem (ES) cells. As discussed above, it is widely recognized in the art that mouse ES cells are uniquely suited to cloning methods involving nuclear transplantation and that, in light of this, one of skill in the art would recognize that procedures involving such cells could not be transferred to somatic cells with any degree of predictability. Thus, the combination of references cited against the claims under §103(a) fall far short of leading one of ordinary skill in the art to the practice of the present invention. In summary, Cibelli et at disclose merely the incubation of nuclear transfer embryos for 6.5 days after nuclear transplantation and do not address in any way the feasibility of culturing donor cells for 30 or more days prior to implantation in recipient oocytes. The relevant teachings of the Plump *et al.* and Arbones *et al.* references, in that they are specifically directed to mouse ES cells, are inapplicable to the somatic cells of the claimed invention. To the extent that The Arbones *et al.* reference addresses long-term culture (100 doublings) it does nothing more than recite what is accepted in the art - that multiple doublings of genetically transformed cells promotes the confirmation of such genetic alterations. These teachings do nothing to instruct on using genetic material from such long-term culture as donor material in successful nuclear transfer cloning. Accordingly, Applicants respectfully submit that the cited rejection under §103(a) has been overcome and request withdrawal of same.

CONCLUSION

Based on the Remarks as submitted above, Applicants respectfully suggest that the claims as amended are in condition for allowance, which action is respectfully requested.

Respectfully submitted,



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